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Thrombolytics in Cardiac Arrest from Pulmonary Embolism: A Systematic Review and Meta Analysis

Jordan Feltes[1], Margarita Popova[1], Yasir Hussein[1], Ayal Pierce[1], and David Yamane[1,2]

Abstract

Background: During cardiopulmonary resuscitation, intravenous thrombolytics are commonly used for patients whose underlying etiology of cardiac arrest is presumed to be related to pulmonary embolism (PE).

Methods: We performed a systematic review and meta-analysis of the existing literature that focused on the use of thrombolytics for cardiac arrest due to presumed or confirmed PE. Outcomes of interest were return of spontaneous circulation (ROSC), survival to hospital discharge, neurologically-intact survival, and bleeding complications.

Results: Thirteen studies with a total of 803 patients were included in this review. Most studies included were single-armed and retrospective. Thrombolytic agent and dose were heterogeneous between studies. Among those with control groups, intravenous thrombolysis was associated with higher rates of ROSC (OR 2.55, 95% CI = 1.50–4.34), but without a significant difference in survival to hospital discharge (OR 1.41, 95% CI = 0.79–2.41) or bleeding complications (OR 2.21, 0.95–5.17).

Conclusions: Use of intravenous thrombolytics in cardiac arrest due to confirmed or presumed PE is associated with increased ROSC but not survival to hospital discharge or change in bleeding complications. Larger randomized studies are needed. Currently, we recommend continuing to follow existing consensus guidelines which support use of thrombolytics for this indication.

Keywords

cardiac arrest, antithrombotic drugs, critical illness, outcomes, resuscitation

Introduction

There are more than 356,000 out-of-hospital cardiac arrests (OHCA) in the United States per year, of which nearly 90 percent are fatal.[1] Among cardiac arrests, approximately two to ten percent are attributed to pulmonary embolism (PE).[2–5] In practice, diagnosing the cause of a cardiac arrest during resuscitation is extremely difficult. For decades, providers have been administering intravenous thrombolytics in cardiac arrest due to suspected or confirmed PE. Rationale for their use stems from expert opinion on the theoretical benefit of thrombolytics in this clinical scenario as well as promising data for administration of thrombolytics in treatment of massive PE with a detectable pulse.[6]

In subsequent years, there have been several randomized control trials evaluating the use of intravenous thrombolytics during resuscitation in all-cause cardiac arrest, which did not show a survival benefit.[7–10] Subgroup analyses of these trials, while underpowered, trended toward improved survival for PE patients, which is a promising but only hypothesis-generating outcome.

The practice of systemic thrombolysis in cardiac arrest from known PE is backed by ACLS and American Heart Associate (AHA) guidelines, and ILCOR recommendations.[11,12] However, their guidelines note there is no evidence available to support or refute the effectiveness of empiric thrombolysis in suspected but unconfirmed PE.[13] As such, newer AHA recommendations identify the utility of thrombolytics in patients with cardiac arrest due to suspected PE as a pertinent knowledge gap necessitating more research.[14]

Thereafter, there have been several additional studies including larger retrospective cohorts that may provide new evidence for or against the use of thrombolytics in this population. This article systematically reviews the current evidence behind the use of IV thrombolytics in cardiac arrests in adults specifically due to suspected or confirmed pulmonary emboli. We focus on survival to hospital discharge (STHD), neurologically-intact survival (NIS), and bleeding complications.

Methods

We used PRISMA guidelines as the framework for our systematic review. We worked with a medical librarian to conduct a PubMed

[1]Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[2]Department of Anesthesiology and Critical Care Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, USA

Corresponding Author:
Jordan Feltes, Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington, 2120 L St, NW, Suite 450, DC, USA.
Email: feltesjordan@gmail.com

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search of articles that included the keywords of "TPA", "Pulmonary Embolism", and "Cardiac Arrest", along with associated MeSH terms. Our search was limited to studies in English or with English translation. We included studies published at any time up until October 2021, when the search was conducted.

Covidence systematic review manager was utilized to screen abstracts and full-text articles. Studies were screened first by abstract and then by full-text review by at least two reviewers independently (among JF, YH, and MP). Any disagreements were resolved by group discussion and inter-rater reliability was monitored.

In terms of study design, we included randomized control trials (RCTs), prospective cohort studies, and retrospective cohort studies. Case reports and case series were excluded. Both OHCA and in-hospital cardiac arrest (IHCA) patient populations were included. We included studies that evaluated the primary or secondary outcomes of return of spontaneous circulation (ROSC) and/or survival to hospital discharge. Secondary outcomes of interest included bleeding complications and NIS (typically measured via Cerebral Performance Category).

To assess for risk of bias, we used the Cochrane Risk of Bias Tool for randomized trials and ROBINS-I for non-randomized observational studies. Results of a bias assessment for each publication can be seen in Table 1.

For our meta-analysis, we considered the outcomes of ROSC, Survival to Hospital Discharge, and Bleeding Complications. Studies were included in each individual analysis if they included both a control and intervention group. We used R statistical software using the "meta" package for calculating odds ratios. A random effects model was used to generate pooled odds ratios.

Results

Summary of Methods

The initial literature search yielded 2,866 unique studies. At least two reviewers independently evaluated each article based on abstract review to develop a list of 28 potentially relevant studies that were then narrowed to a final list of 13 by full-text review by two reviewers (Figure 1).

During the full-text review, we eliminated 15 studies, primarily due to study design of case reports, case series, and editorials or otherwise not primary research. We also eliminated two studies that did not have the outcomes of ROSC or Survival to Hospital Discharge.[15,16] One additional study was excluded due to their patient population including all-cause cardiac arrest without stratifying patients with pulmonary embolism associated arrest and another due to including only pediatric patients.

There was a 96.4% inter-rater reliability (IRR) in abstract screening and 83% IRR for full text screening and conflicts were resolved via consensus from all reviewers.

Summary of Results

Out of the thirteen studies included, twelve were retrospective reviews and one was prospective RCT that met our inclusion criteria based on one of their subgroup analyses.[7] There were a total of 803 patients in this review with an average of 62 patients (SD = 63) per included study.

Thrombolytic of choice included alteplase in at least ten of the studies, with tenecteplase included in four studies, streptokinase and monteplase in one study each, and two articles did not specify the thrombolytic used. Among studies using alteplase, authors used a single 50- or 100-mg bolus as the most common dosing strategies and less commonly included weight-based dosing or bolus followed by slower intravenous infusion.

Outcomes of Interest

Out of thirteen studies in our final analysis, all studies included the primary or secondary outcome of ROSC and eleven included primary or secondary outcome of survival to hospital discharge.

Among non-randomized studies which were multi-armed and contained a comparator group of patients who did not receive thrombolytics during resuscitation.[4,5,7,17–20] only Kürkciyan et al. found a difference in ROSC that favored the intervention group, whereas the other five of six that measured ROSC found no difference, and none favored placebo. Despite this, in our meta-analysis, ROSC was overall more common in the thrombolytic groups than control groups (OR 2.55, 95% CI = 1.50–4.34) [Figure 2].

Within these studies, survival to hospital discharge was measured in five studies and differed between intervention and non-intervention groups in only one.[4] When pooling all studies, there was no difference in survival to hospital discharge associated with thrombolytic use (OR 1.41, 95% CI = 0.79–2.41) [Figure 3]

In terms of secondary outcomes, seven of thirteen studies included the outcome of major bleeding complications. Interestingly, the most common bleeding complication described was intra-abdominal bleeding, including perirenal hemorrhage and liver hematoma or rupture. The next most common bleeding complication was central-line associated bleeding, and less commonly present were intracranial and intrathoracic hemorrhage. In our meta-analysis, there was a trend toward increased number of major bleeding events in the thrombolysis group, though not statistically significant (OR 2.21, 0.95–5.17) [Figure 4].

Four studies included the outcome of neurologically-intact survival. NIS was measured most commonly by the Cerebral Performance Category (CPC) score and good neurologic outcome defined as CPC less than three, representing at most moderate cerebral disability, which is defined as "disabled but independent". Only two of the multi-armed studies[18,20] evaluated NIS and neither found a difference in this outcome between thrombolytic and non-thrombolytic groups.

Bias was determined to be moderate to high for most studies included. Major contributors to bias included non-consecutive or poorly described enrollment methods, differences in baseline patient characteristics, retrospective nature of data collection, and one manufacturer-sponsored study.

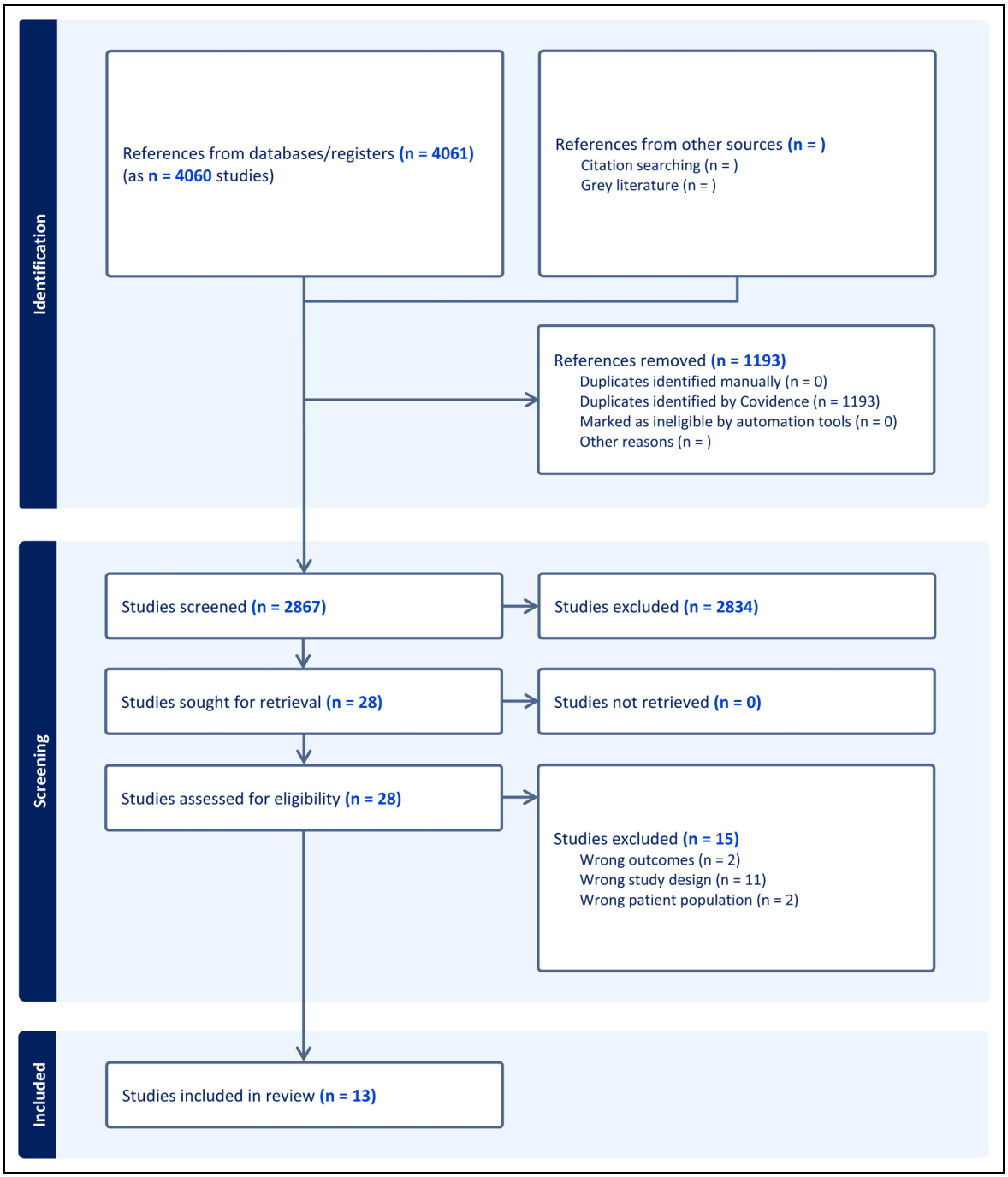
Discussion

Interpretation of Results

This systematic review and meta-analysis summarizes the literature that currently exists evaluating the use of thrombolytic

Table 1. Individual studies included in review.

Authors	Year	Study Type	Subgroup Analysis	Thrombolytic	Patients	ROSC	Survival to Hospital Discharge	Neurologically-Intact Survival	Major Bleeding Complications	Risk of Bias
Kürkciyan et al.	2000	Retrospective cohort	No	Alteplase (100 mg bolus)	42	81% (17/21) vs 43% (9/21)	10% (2/21) vs 5% (1/21)	NA	24% (5/21) vs 0% (0/21)	Serious
Yousuf et al.	2016	Retrospective cohort	No	Alteplase (100 mg bolus)	42	47% (9/19) vs 48% (11/23)	11% (2/19) vs 9% (2/23)	NA	5% (1/19) vs 4% (1/23)	Moderate
Bougouin et al.	2017	Prospective cohort	No	Unspecified	82	N/A	30% (14/47) vs 15% (5/35)	NA	NA	Serious
Dirican et al.	2014	Single-arm retrospective review	Yes	Alteplase (10 mg bolus + 90 mg infusion)	11	N/A	36% (4/11)	NA	NA	Serious
Niwa et al.	2012	Single-arm retrospective review	Yes	Monteplase	85	Unknown	41.2% (35/85) [30 day survival]	NA	NA	Serious
Sharifi at al.	2016	Single-arm retrospective chart review with prospective follow up	No	Alteplase (50 mg)	23	100% (23/23)	91% (21/23)	91% (21/23)	NA	Serious
Er et al.	2009	Single-arm retrospective review	No	Alteplase	104	38% (40/104)	18% (19/104)	13% (14/104)	23% (9/40)	Moderate
de Paz et al.	2021	Retrospective cohort	No	Unspecified	16	100% (8/8) vs 88% (7/8)	62% (5/8) vs 62% (5/8)	100% (3/3) vs 100% (3/3)	25% (2/8) vs 0% (0/8)	Moderate
Janata et al.	2003	Retrospective cohort	No	Alteplase (0.6–1.0 mg/kg)	66	67% (24/36) vs 43% (13/30)	19% (7/36) vs 7% (2/30)	NA	25% (9/36) vs 10% (3/30)	Serious
Kataria et al.	2021	Single-arm retrospective review	No	Alteplase (50 mg or 100 mg) or Tenecteplase	27	41% (11/27)	2/27 (7%)	NA	1/11 (9%)	Moderate
Javaudin et al.	2019	Retrospective cohort	No	Alteplase, Tenecteplase, Streptokinase	246	16% (9/58) vs 12/188 (6%)	NA	10% vs 5%	6% (3/58) vs 5% (9/188)	Low
Summers et al.	2019	Single-arm retrospective review	No	Alteplase (100 mg) or Tenecteplase (0.5 mg/kg)	22	50% (11/22)	14% (3/22)	NA	0% (0/22)	Moderate
Böttiger et al.	2008	Double-blind multicenter RCT	Yes	Tenecteplase (0.5 mg/kg)	37	13% (2/15) vs 0% (0/22)	NA	NA	NA	Low


Identification
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(as n = 4060 studies)
References from other sources (n =)
Citation searching (n =)
Grey literature (n =)
References removed (n = 1193)
Duplicates identified manually (n = 0)
Duplicates identified by Covidence (n = 1193)
Marked as ineligible by automation tools (n = 0)
Other reasons (n =)
Screening
Studies screened (n = 2867)
Studies excluded (n = 2834)
Studies sought for retrieval (n = 28)
Studies not retrieved (n = 0)
Studies assessed for eligibility (n = 28)
Studies excluded (n = 15)
Wrong outcomes (n = 2)
Wrong study design (n = 11)
Wrong patient population (n = 2)
Included
Studies included in review (n = 13)

Figure 1. Flow diagram of systematic review process and exclusions.

agents in cardiac arrest for presumed or confirmed PE. Most studies were either retrospective reviews, prospective observational trials, or subgroup analyses of larger RCTs. There are no prospective randomized controlled trials available that specifically focus on pulmonary embolism and cardiac arrest.

Among the individual studies with control groups, only Kürkciyan et al reported a statistically significant difference in ROSC based on their primary data interpretation (81% vs 43%; $p = 0.03$).[5,7,18–20] Other studies did trend towards favoring thrombolytics over control for achieving ROSC, though were underpowered to detect a statistically significant difference in outcomes. Specifically, the 37-patient subgroup of the Böttiger et al RCT included in this review was one of the first to hypothesize that patients with pulmonary embolism may have better outcomes after systemic thrombolysis than patients with all-cause cardiac arrest. However, their subgroup failed to achieve a statistically significant difference in ROSC because the study was not initially powered to address this question.

When evaluated together, there were higher rates of ROSC in the group that received thrombolytics as compared to

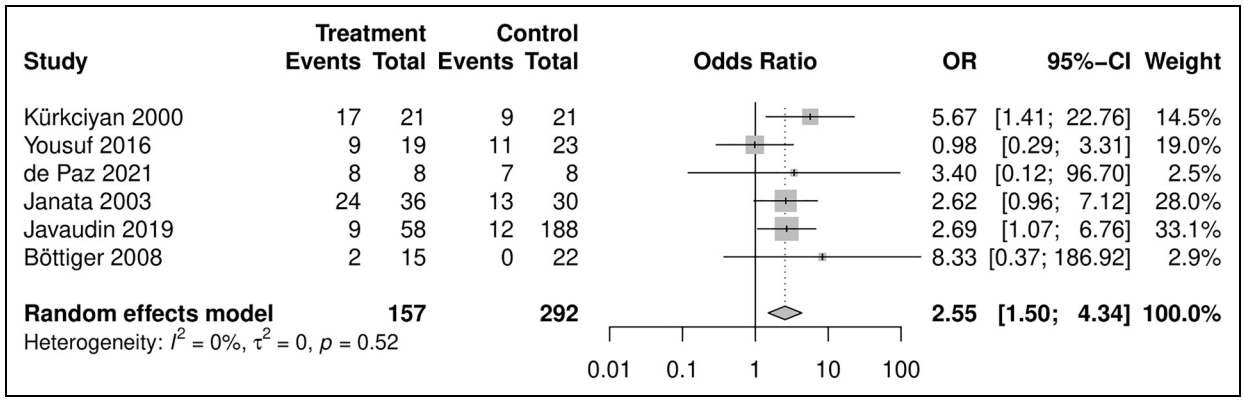

Figure 2. Return of Spontaneous Circulation among studies that included both control and treatment arms.

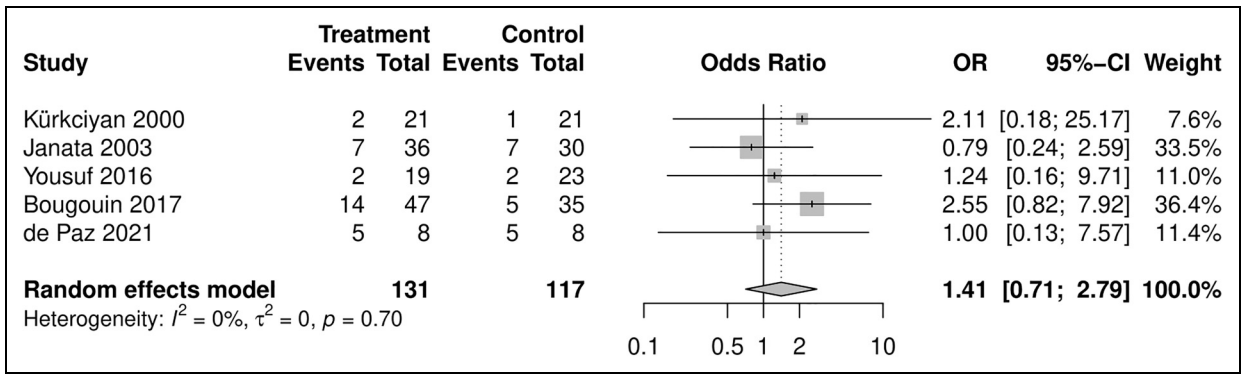

Figure 3. Survival to Hospital Discharge among studies that included both control and treatment arms.

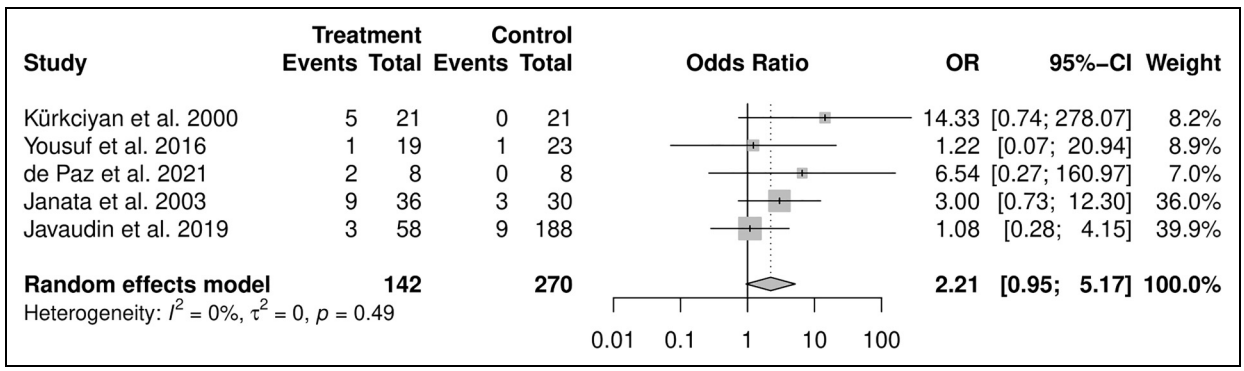

Figure 4. Bleeding Complications among studies that included both control and treatment arms.

controls, though aggregated data were heavily influenced by the 2019 Javaudin study, as it contained approximately 55% of all patients included in this analysis.

Bougouin et al was the only study included that reported a significant difference in survival to hospital discharge (30% vs 15%; p = 0.01). The major limitation of this study was its observational, non-randomized nature which may introduce bias and that enrollment only included patients who had already achieved ROSC. Together, the available studies that evaluated STHD showed no difference for patients receiving thrombolytics.

In terms of our secondary outcome of major bleeding events, we note that major bleeding events reported were more common in thrombolysis arms. However, bleeding complications described were mostly non-fatal and primarily included intra-abdominal bleeding and line-associated bleeding, with less common instances of ICH and intra-thoracic hemorrhage. There is no evidence suggesting increased mortality associated with bleeding adverse events in pulmonary embolism with hemodynamic collapse, which is different than the generally accepted risk of major intracranial bleed of ~6% when using relatively similar doses of IV thrombolytics for patients with

ischemic stroke.[21–23] This may be explained by lack of structural intracranial pathology within the population of patients with life-threatening PEs as compared to patients with large ischemic strokes who may have pre-existing atherosclerosis and other structural vascular changes that predispose to hemorrhagic conversion.

This review is consistent with but builds upon prior analysis of thrombolytics in cardiac arrest. Notably, AHA guidelines from 2015 to 2020 as well as Logan et al. from 2014 which had a similar scope to this review.[24]

Limitations of Review Process and Limitations of Contributing Studies

Studies included were heterogeneous in both methods and outcomes of interest. From a methodological standpoint, the thrombolytic used varied between alteplase, tenecteplase, monteplase, and streptokinase. Thrombolytics were dosed in both fixed dose and weight-based regimen and infrequently used a continuous drip following initial.[25] This limits the internal validity of aggregate results obtained from our meta-analysis. Additionally, neurologically-intact survival, arguably more clinically significant than all-cause survival, was absent from more than half of included studies.

Another significant limitation is that the majority of individual studies included patients who had suspected and not confirmed pulmonary emboli. There is a high likelihood that some patients included in these groups did not actually have pulmonary emboli or that PE was not the primary cause of cardiac arrest, which would skew away from a positive treatment effect. However, including suspected pulmonary emboli associated cardiac arrests are more relevant to the treating clinician than just including confirmed cases, as in the majority of cardiac arrests, there is no definitive etiology of the arrest available during the initial resuscitation when the decision to use thrombolytics is made. Retrospective reviews have been conducted evaluating the test characteristics of using either pre-arrest symptoms or post-arrest echocardiography to develop clinical decision tools for diagnosing PE at the bedside in cardiac arrest patients, however, sensitivity has been low and these tools have not yet been externally validated.[26,27]

Our review process was limited by several factors including limiting available search to studies written in English or with English translations and using PubMed as our primary database. We also limited ourselves to use of only the publicly available data from each published study and did not reach out to individual authors for additional information. Review was not registered.

Conclusions

Clinical Implications of Results

Overall, this systematic review and meta-analysis provide limited evidence supporting the use of intravenous thrombolytics in cardiac arrest from presumed or confirmed PE. Due to the observational nature of the studies included in this review as well as their risk of bias, further prospective randomized controlled trials are needed. We recommend continuing to follow existing consensus guidelines which support use of thrombolytics for this indication.

Declarations of Interest

None

ORCID iD

Jordan Feltes https://orcid.org/0000-0002-5944-3266

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